

SYSTEMATIC REVIEW

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Clinical features and outcomes of persons with cystic fibrosis and nocardia isolation: a systematic review

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Abstract

Background Recurrent respiratory infections are a leading cause of morbidity and mortality in persons with Cystic Fibrosis (pwCF). Recently, the emergence of *Nocardia* species as a potential pathogen in CF has raised questions about its role and management, as its clinical significance and the optimal patient management remain unclear in current clinical practice. This review explores the clinical implications of *Nocardia* species in patients with Cystic Fibrosis (pwCF) through a comprehensive literature review. Key objectives include assessing its impact on lung function, identifying colonization risk factors, and evaluating an appropriate treatment.

Methods The literature review, conducted until June 30, 2023, from databases like MEDLINE, PubMed, Embase, and Cochrane, included 16 articles involving 89 pwCF with *Nocardia* species isolation according to the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) guideline recommendations. Articles reporting *Nocardia* prevalence and symptoms based on original data in adult and paediatric pwCF were included. All the retrieved studies were observational ones, thus, they were categorized by study type as case report and case series.

Results Overall 89 pwCF and *Nocardia* species isolation were included: 42 children and 47 adults. Where reported, we found these main following bacterial species: *Nocardia asteroides* (35%, 23/64), *Nocardia farcinica* (21%, 14/64), *Nocardia tranvalensis* (13%, 8/64) and *Nocardia cyriacigeorgica* (11%, 7/64). A co-infection was reported in 85% of patients (61/72). Of patients whose lung function was reported before and after *Nocardia* isolation, 23% (16/68) showed a decline in FEV₁. Above all, 82 patients were treated at least once after isolation of *Nocardia* strain. In 93% (77/82) of cases, treatment was started immediately upon isolation. Antibiotic treatment was performed *per os* or intravenously depending on the clinical condition of the individual patient. *Nocardia* eradication was attempted in only 32 cases out of 82, and 78% (25/32) of these patients were successfully eradicated after one or more courses of antibiotics. Death was reported in 3 patients, 2 of which were children.

Conclusion In general the isolation of the bacteria does not necessarily imply therapy, but patients need to be monitored closely to assess the possible occurrence of active infection. The treatment seems to be indicated in

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patients showing lung involvement with the possible appearance of pneumonia, pleural effusion, fever, cough, or a decrease in FEV₁, as in the case that we described, or in patients undergoing pulmonary transplantation.

Strengths and limitations of this study

- A strength of this study is that it provides an updated systematic review on the management of *Nocardia*'s isolation in patients with Cystic Fibrosis. By synthesising findings across all included studies we propose a therapeutic management algorithm.
- This systematic review protocol follows the Joanna Briggs Institute, mixed-method systematic review protocol.
- Limitations of the study is the paucity of randomised controlled trials and the heterogeneity among available publications.
- There is potential for heterogeneity of published data, which may limit the conclusions that can be drawn from this study.

Keywords FEV1, Lung transplantation, Therapy, Eradication, Children

Introduction

Cystic fibrosis (CF) is a common autosomal recessive disorder resulting from variants in the CF transmembrane conductance regulator (*CFTR*) gene. Multiple systems are affected, however, respiratory tract infections are one leading cause of morbidity and mortality [1].

The adaption of 16s rDNA community sequencing technologies and more extensive culturing approaches [2] have enabled the identification of bacterial strains in the pulmonary microbiota only recently considered to potentially have a pathogenic role including members of the genera *Bacteroides*, *Gemella*, *Prevotella*, *Sphingobacterium* and *Nocardia* spp [9–15].

Specifically for *Nocardia*, a large number of species have been recognized with different geographic prevalences, pathogenic traits, and antimicrobial susceptibility patterns [5]. Therefore, the identification of *Nocardia* isolates to the species level might provide physicians with useful information but only limited laboratories have the necessary facilities [5]. *Nocardia* spp are a gram-positive aerobic filamentous bacteria, ubiquitous in soil and aquatic habitats and worldwide spread. Transmission occurs mainly by inhalation of organisms contained in the dust, but also, more rarely, by skin inoculation directly through a wound [3–6].

Nocardial infection may be associated to lung or skin disease and, especially in immunocompromised patients, it may disseminate and virtually involve any body site, including the central nervous system (CNS) where brain abscesses may occur, while meningitis is rarely seen [4, 6].

Pulmonary nocardiosis can manifest as acute, sub-acute, or chronic disease. Symptoms of nocardiosis are unspecific and may include fever, dyspnea, chest pain, increased respiratory secretions and night sweats [4, 6]. X-ray shows multiple lung infiltrates, rarely associated with necrotizing pneumonia. Chest radiograph can demonstrate areas of consolidation, mild diffuse infiltrates, reticulonodular patterns, or cavitation [6]. According to some experts' opinion, if *Nocardia* species are identified

in CF sputum, his clinical significance and the optimal patient management remain unclear [9–19]. Determining the difference between *Nocardia* infection versus colonization is extremely challenging in CF patients due to several reasons: the inconsistency of patient's clinical symptoms, the absence of pathognomonic radiological features, the difficulty in identifying this slow-growing microorganism on common culture media (although nowadays the use of non-culture methods such as NGS (Next-Generation Sequencing) and PCR (Polymerase Chain Reaction), where applicable, have resolved this issue), the lack of understanding of its role in the microbiota of the lung in a patient with CF. Furthermore, *Nocardia* species are often found alongside other microorganisms. Moreover, to complicate the picture, adverse events to antibiotic therapy may occur and appropriate duration of therapy in these patients is under debate [8–10, 15].

With this systematic review, our aim is to examine the current understanding of the clinical implications of *Nocardia* species in individuals with CF, starting from the presentation of a clinical case. Moreover, a systematic literature review was performed in order to evaluate the management of *Nocardia* isolation and outcomes in patients with CF. Finally, we attempt to address some of the questions that clinicians might face when encountering this unconventional bacterium in the respiratory tracts of pwCF.

Review questions

- Do *Nocardia* species have a pathogenic role in patients with CF?
- What are the risk factors for nocardiosis in pwCF?
- Does *Nocardia* affect lung function in pwCF?
- Should pwCF with *Nocardia*-positive sputum always be treated?
- What antibiotic regimen should be used in pwCF?

- How long should the antibiotic treatment for *Nocardia* last in pwCF?

Inclusion and exclusion criteria

Articles reporting *Nocardia* prevalence and symptoms based on original data in adult and paediatric pwCF were included. Commentaries, editorials and letters to the author with no original data were excluded as well as studies concerning *Nocardia*'s infection in persons who did not have CF. No restrictions on language of publication were applied.

Methods and analysis

We performed a systematic review of the literature, according to the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) guideline recommendations.

Search strategy

We searched the MEDLINE by PubMed, Embase and Cochrane databases for articles available up to 30 June 2023. Search terms for the MEDLINE and EMBASE database were: ("Nocardiosis" [All Fields] OR "Cystic Fibrosis" [All Fields] OR "Nocardiosis isolation" [All Fields] OR "Nocardiosis treatment" [All Fields] OR "Nocardiosis prognosis" [All Fields] OR "Infections in pwCF" [All Fields]).

Study selection

At first, we screened titles and abstracts to discover eligible studies, and then we analyzed all full texts for the final evaluation. Two investigators (TB, AC) independently reviewed and evaluated every study. Studies were limited to human participants and of any follow-up duration and timepoints. The quality of the eligible studies was evaluated by two authors independently (TB, AC), using different methods according to the study design: The Joanna Briggs Institute (JBI) Critical Appraisal Checklist for Case Reports [16] and the Joanna Briggs Institute (JBI) Critical Appraisal Checklist for Case Series [17]. We planned to use the Newcastle-Ottawa Quality Assessment Form for the analytic observational studies [18], however, we did not identify articles that properly fitted this definition.

Data extraction

From each study, we selected information regarding study design, date of publication, country of origin, age at first *Nocardia*'s isolation, *Nocardia*'s species, co-infections, reported symptoms, deaths related to *Nocardiosis*, patients for whom FEV1 has worsened, type of treatment and the number of eradicated patients. All key extracted data were reviewed and quality checked at the end of the data extraction phase by the same two researchers. All

the retrieved studies were observational ones, thus, they were categorized by study type as case report and case series.

Results

Literature review

Included studies

The process of selecting included studies is shown in the Fig. 1.

Overall, 41 articles were initially retrieved; a total of 16 articles were eligible according to our criteria and were included in the review: 9 case reports and 7 case series.

Characteristics of the included studies are reported in Table 1.

Quality assessment

The quality assessment of the studies is reported in Figs. 2 and 3.

Quality assessment of the included studies. Figure 2: The Joanna Briggs Institute (JBI) Critical Appraisal Checklist for Case Reports; Fig. 3: The Joanna Briggs Institute (JBI) Critical Appraisal Checklist for Case Series.

Outcomes

Overall, 89 pwCF and *Nocardia* species isolation were included: 42 children and 47 adults. Among the 71 patients whose sex was specified, 32 were female (45%) and 39 were male (55%). Where reported, we found the following bacterial species: *Nocardia asteroides* (35%, 23/64), *Nocardia farcinica* (21%, 14/64), *Nocardia tranvalensis* (13%, 8/64), *Nocardia cyriacigeorgica* (11%, 7/64), *Nocardia abscessus* (5%, 3/64), *Nocardia veterana* (3%, 2/64), *Nocardia wallacei* (3%, 2/64), *Nocardia miyunesis* (1%, 1/64), *Nocardia pneumoniae* (1%, 1/64), *Nocardia asiatica* (1%, 1/64), *Nocardia elegans* (1%, 1/64), *Nocardia otitidiscavarium* (1%, 1/64). A co-infection was reported in 85% of patients (61/72). In 17 patients the possible presence of other microorganisms in sputum was not mentioned.

Of patients whose lung function was reported before and after *Nocardia* isolation, 23% (16/68) showed a decline in FEV₁.

Above all, 82 patients were treated at least once after isolation of *Nocardia* strain. In 93% (77/82) of cases, treatment was started immediately upon isolation.

Antibiotic treatment was performed *per os* or intravenously depending on the clinical condition of the individual patient. The following antibiotics were prescribed in the 16 selected articles: trimethoprim-sulfamethoxazole (52/82, 63%), ciprofloxacin (17/82, 20%), penicillins (16/82, 18%), aminoglycosides (12/82, 14%), cephalosporins (11/82, 13%), carbapenems (10/82, 12%), tetracyclines (8/82, 10%), linezolid (7/82, 9%). For 30 out of 89

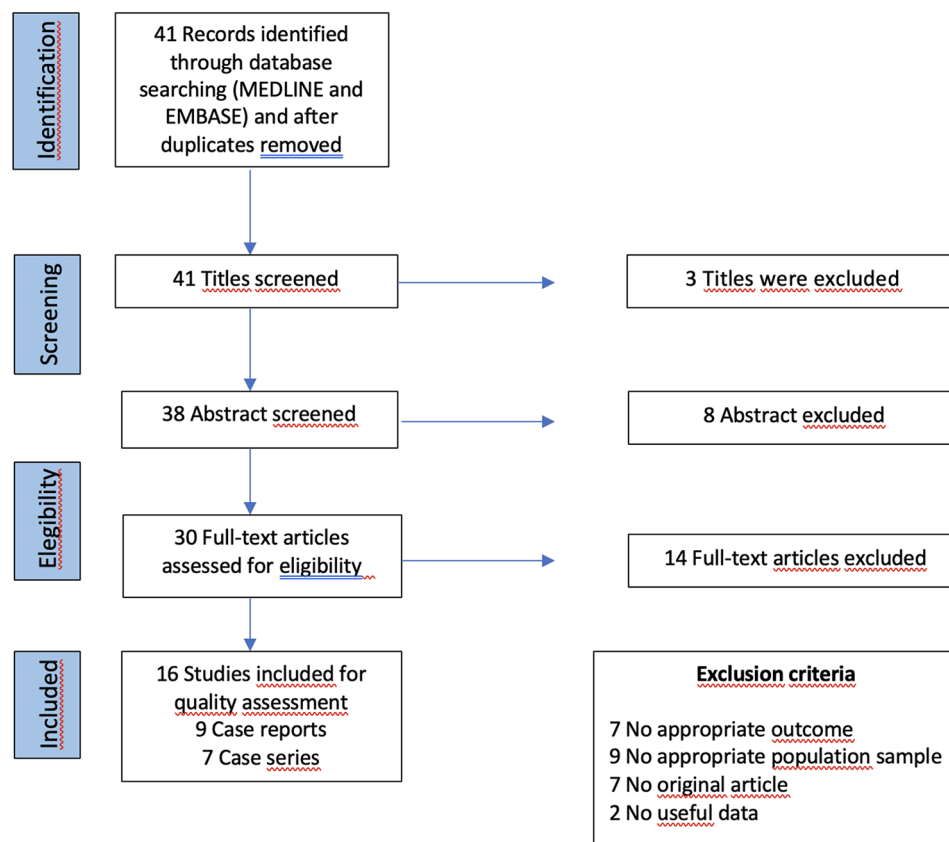


Fig. 1 flow chart of the study selection

patients (33%), hospitalization and intravenous antibiotic therapy were required. Death was reported in 3 patients, 2 of which were children, with severe lung disease or Pa and Mycobacterium avium complex co-infection.

Nocardia eradication was attempted in only 32 cases out of 82, and 78% (25/32) of these patients were successfully eradicated from *Nocardia* after one or more courses of antibiotics.

The results of the studies have been reported in the Table 1.

Discussion

Do *Nocardia* species have a pathogenic role in patients with CF?

The pathogenic role of *Nocardia* in pwCF is still unclear [10, 15]. In 2002, Lumb et al., in a retrospective study on 3 pwCF, firstly discussed the role of *Nocardia* as a possible pathogen in CF, concluding that the isolation of this bacteria does not always mean active infection. Therefore, the treatment must be considered in the clinical context of each patient and a careful follow-up is mandatory, particularly in patients in therapy with steroids due to their immunosuppressive effect [8]. This view was confirmed by subsequent studies. In 2009 Thorn et al., in a retrospective study on 17 pwCF, concluded that

Nocardia frequently acts as a colonizer, not resulting in active infection with symptoms or impaired respiratory function [10]. Our study confirms this variability in the pathogenicity of *Nocardia* across various studies and suggests a clinically guided approach based on imaging and lung function.

What are the risk factors for nocardiosis?

In the previously mentioned study by Lumb et al., the authors associate nocardiosis with cell-mediated immunosuppression, potentially facilitated by corticosteroid oral treatment or a history of transplantation [8, 9, 13, 19]. Others link nocardiosis to the co-colonization of *Nocardia* species and Pa [10], although this observation is strictly clinical and contradicted by other case series studies [15, 22], or highlight a history of bronchopulmonary aspergillosis (ABPA) as a high risk to develop lung disease in CF patients with *Nocardia* species [21]. Similarly, *Nocardia* can be damaging in patients undergoing lung transplantation, resulting in rapid failure of respiratory function, as described by Chacon et al. in 2014 [19]. Some authors correlate the subspecies of *Nocardia transvalensis* with a greater symptom burden than the more prevalent *Nocardia asteroides* subspecies [20]. *Nocardia* isolations are typically uncommon in the general

Table 1 Literature reviews's results

	Patient, sex, mean age at first isolation of No-cardia species (years)	Species	Other microorganisms isolated	Clinical symptoms	Worsening FEV1 after No-cardia species isolation (Death †)	Antibiotics prescribed	No-cardia eradication
Yagupsky et al., 1994, Case report, Israel	M, 6 yy	N. Asteroides	Pseudomonas Aeruginosa, S. Aureus	Fever Cough Hypoxia	Not reported	Trimetoprim-sulfometoxazole	Not reported
Lumb et al., [8], Case series, Australia	3 patients, 2 M, 1 F, 25.3 yy	N. Asteroides (3/3)	P. Aeruginosa (2/3)	Exacerbation of respiratory symptoms (1/3) Asymptomatic (2/3)	Yes (1/3) † (1)	Trimetoprim-sulfometoxazole (3/3)	Yes (2/3)
Petersen et al., [9], Case report, USA	5, M, 8 yy	N. Farcinica	S. aureus, A. fumigatus	Fever, cough	Not reported	Trimetoprim-sulfometoxazole	No
Barrio et al., [10], Case series, Spain	9 patients, 1 M, 8 F, 16.6 yy	N. Asiatica (1/9) N. Asteroides (2/9) N. elegans (1/9) N. farcinica (1/9) N. transvalensis (1/9) Not reported (3/9)	P. Aeruginosa (7/9), S. Aureus (5/9) S. Maltophilia (2/9) H. Influenzae (3/9) C. Albicans (1/9) A. Fumigatus (2/9), Achromobacter xylosoxidans (1/9)	Fever, dyspnea, chest pain, hemoptysis, cough Asymptomatic (3/9)	Not reported	Trimetoprim-sulfometoxazole (6/9) Aminoglycosides (1/9) Tetracyclines (2/9) Carbapenems (1/9) No treatment (2/9)	Yes (9/9)
Thorn et al., [11], Case series, USA	17 patients, 6 F, 11 M, 24,7 yy	N. Asteroides (14/17), N. farcinica (1/17), N. cyriaciogeorgica (1/17), N. otitidiscavarium (1/17)	Unknown	Unknown	No	Trimetoprim-sulfometoxazole (13/17) Tetracyclines (3/17) No treatment (1/17)	Not reported
Beucher et al., 2009, case report, France	M, 20 yy	N. Farcinica	None	Fever, dyspnea, skin nodular eruption	Yes †	Trimetoprim-sulfometoxazole Aminoglycosides	No
Bittar et al., [13], case report, France	M, 15 yy	N. Farcinica	S. Aureus H. Influenzae	Fever (39 °C), fatigue, haemoptysis, bronchial syndrome, and respiratory decompensation	Not reported	Trimetoprim-sulfometoxazole Aminoglycosides Ciprofloxacin	Not reported
Aravantiagi et al., [14], case report, USA	M, 19 yy	N. Transvalensis	P. Aeruginosa	Respiratory decompensation	Yes	Trimetoprim-sulfometoxazole Linezolid	Yes
Rodriguez-Nava et al., [15], Case series, France	16 patients, 11 M, 5 F, 22.6 yy	N. Cyriaciogeorgica (8/16) N. Farcinica (3/16) N. abscessus (3/16) N. veterana (1/16) N. wallacei (1/16) Not reported (1/16)	S. aureus (8/16) S. maltophilia (3/16) H. influenzae (1/16) S. pneumoniae (1/16) P. Aeruginosa (3/16) Candida Albicans (2/16) A. fumigatus (5/16) None (6/16)	Cough Weight loss Dyspnea Fever Asthenia Chest pain Asymptomatic (3/16)	Yes (5/16)	Trimetoprim-sulfometoxazole (6/16) Aminoglycosides (3/16) Penicillines (5/16) Cephalosporins (2/16) Ciprofloxacin (2/16) Linezolid (3/16)	Not reported

Table 1 (continued)

	Patient, sex, mean age at first isolation of Nocardia species (years)	Species	Other microorganisms isolated	Clinical symptoms	Worsening FEV1 after Nocardia species isolation (Death †)	Antibiotics prescribed	No-cardia eradication
Chacon et al., [19], case report, Spain	F, 26 yy	<i>N. farcinica</i>	<i>A. Fumigatus</i>	15 dd after lung transplantation: respiratory decompensation	Not reported	Trimetoprim-sulfamethoxazole Aminoglycosides Carbapenems Ciprofloxacin Linezolid	Yes
Schoen et al., [20], case report, USA	F, 9 yy	<i>N. transvalensis</i>	None	Respiratory decompensation	Yes	Trimetoprim-sulfamethoxazole Penicillines Cephalosporins Linezolid	Yes
Meir Mei-Zahav et al., [21], Case series, Israel	8 patients, 5 M, 3 F, 17.6 yy	<i>N. Asteroides</i> (2/8) <i>N. Cyriacigeorgica</i> (1/8) <i>N. Miyunesis</i> (1/8) Not reported (3/8) <i>N. Farcinica</i> (1/8)	<i>Pseudomonas Aeruginosa</i> (5/8) <i>S. Maltophilia</i> (1/8) None (2/8) <i>A.Fumigatus</i> (1/8)	Fever Cough Weight loss Recurrent febrile episodes, respiratory decompensation Asymptomatic (1/8)	Yes (7/8)	Trimetoprim-sulfamethoxazole (5/8) Aminoglycosides (2/8) Carbapenems (4/8) Penicillines (1/8) Cephalosporins (1/8) Linezolid (2/8)	Yes (5/8)
Adi Dagan et al., [22], Case series, Israel	19 patients, sex unknown, 20.5 yy	Unknown	<i>S. Aureus</i> 7/19, <i>P.Aeruginosa</i> 15/19, <i>Aspergillus</i> sp 12/19, <i>M. abscessus</i> 5/19	Dyspnea, cough, fever, chest pain, and hemoptysis	No	Trimetoprim-sulfamethoxazole (3/19) Aminoglycosides (7/19) Tetracyclines (3/19) Carbapenems (7/19) Penicillines (7/19) Cephalosporins (7/19) Ciprofloxacin (12/19)	Not reported
Betran et al., [23], Case series, Spain	8 patients, 2 M, 6 F, 14.8 yy	<i>N. Farcinica</i> (3/8) <i>N. transvalensis</i> (2/8) <i>N. Veterana</i> (1/8) <i>N. Pneumoniae</i> (1/8) <i>N. Wallacei</i> (1/8) Unknown	<i>S. Aureus</i> (6/8) <i>H. Influenzae</i> (1/8) <i>P. Aeruginosa</i> (6/8) <i>S. apiospermum</i> (2/8) <i>A.Fumigatus</i> (1/8) None	Respiratory decompensation (2/8) Asymptomatic (6/8)	Not reported † (1)	Trimetoprim-sulfamethoxazole (5/8) Penicillines (2/8) Aminoglycosides (2/8) No treatment (2/8)	Yes (5/8)
Eyboğlu et al., [24], case report, Turkey	M, 7 yy	Unknown	None	Fever Cough Dyspnea Evolution to macrophage activation syndrome	Not reported	Penicillines Trimetoprim-sulfamethoxazole Aminoglycosides Carbapenems	Yes
Driscoll et al., [25], case report, United Kingdom	M, 16 yy	<i>N. Farcinica</i>	SARS-CoV2 <i>P. Aeruginosa</i>	Fever, dyspnea, lethargy, hypoxia	Not reported	Trimetoprim-sulfamethoxazole Carbapenems Cephalosporins Ciprofloxacin	No

Q1	Were patient’s demographic characteristics clearly described?
Q2	Was the patient’s history clearly described and presented as a timeline?
Q3	Was the current clinical condition of the patient on presentation clearly described?
Q4	Were diagnostic tests or assessment methods and the results clearly described?
Q5	Was the intervention(s) or treatment procedure(s) clearly described?
Q6	Was the post-intervention clinical condition clearly described?
Q7	Were adverse events (harms) or unanticipated events identified and described?
Q8	Does the case report provide takeaway lessons?

	Yes
	No
	Unclear
	Not applicable
	Unclear setting
	Missing patient information
	Missing information on type/duration/dosage of therapies
	Missing epidemiological information
	Data from multiple Hospitals

The Joanna Briggs Institute (JBI) Critical Appraisal Checklist for Case Reports								
Study	Q1	Q2	Q3	Q4	Q5	Q6	Q7	Q8
Yagunsky et al.		 			 			
Petersen et al.		 						
Beucher et al.					 			
Bittar et al.		 			 	 		
Aravantagi et al.								
Chacon et al.								
Schoen et al.								
Eyboğlu et al.					 			
Driscoll et al.					 			

Fig. 2 Quality assessment of the included studies: the Joanna Briggs Institute (JBI) Critical Appraisal Checklist for Case Reports

Q1	Were there clear criteria for inclusion in the case series?
Q2	Was the condition measured in a standard, reliable way for all participants included in the case series?
Q3	Were valid methods used for identification of the condition for all participants included in the case series?
Q4	Did the case series have consecutive inclusion of participants?
Q5	Did the case series have complete inclusion of participants?
Q6	Was there clear reporting of the demographics of the participants in the study?
Q7	Was there clear reporting of clinical information of the participants?
Q8	Were the outcomes or follow-up results of cases clearly reported?
Q9	Was there clear reporting of the presenting site(s)/clinic(s) demographic information?
Q10	Was statistical analysis appropriate?

	Yes
	No
	Unclear
	Not applicable
	Unclear setting
	Missing patient information
	Missing information on type/duration/dosage of therapies
	Missing epidemiological information
	Data from multiple Hospitals

The Joanna Briggs Institute (JBI) Critical Appraisal Checklist for Case Series										
Study	Q1	Q2	Q3	Q4	Q5	Q6	Q7	Q8	Q9	Q10
Lumb et al.										
Barrio et al.										
Thorn et al.										
Rodriguez-Nava et al.										
Meir Meir-Zahav et al.										
Adi Dagan et al.										
Betran et al.										

Fig. 3 Quality assessment of the included studies: the Joanna Briggs Institute (JBI) Critical Appraisal Checklist for Case Series

pediatric population, and advanced age is recognized as a risk factor for nocardia’s infections. However, our analysis reveals that children contract these infections at a similar rate to adults. These findings might indicate that, in addition to age, CF should be regarded as an additional risk factor [15]. Finally, a recent case report link necrotizing pneumonia to co-infection of *Nocardia* and Covid-19 in pwCF [25].

Does *Nocardia* affect lung function?

In 2015, a longitudinal study examined pulmonary function tests (PFT) in pwCF before and after *Nocardia* isolation not reporting statistically significant difference between patients with a single episode and those with recurrent isolation, nor between patients that underwent antibiotic therapy and those who did not receive treatment. However, pwCF affected by nocardiosis showed a

small trend to faster decline in PFTs compared to similar status CF patients without isolation of this microorganism in their sputum [11, 22]. Other authors noticed *Nocardia* species positive sputum culture may be followed by lung function deterioration and may promote the onset of other infections [21]. Our review demonstrates that only a few patients exhibit a deterioration in lung function following the isolation of *Nocardia*. However, data on lung function trends in these patients are weak in the literature and deserve further investigation.

Should patients with *Nocardia*-positive sputum always be treated?

At the present there are no guidelines for treatment of *Nocardia* in pwCF and the most prudent strategy seems to be the one suggested by Barrio et al. in a retrospective study in 2008: the isolation of *Nocardia* does not necessarily imply therapy and patients need to be monitored closely to assess the possible occurrence of active infection and subjects to be treated should be selected on an individual basis [10].

A proposal for a therapeutic management algorithm is reported in Supplemental Figure S1. Antibiotic treatment should always be administered when *Nocardia* species are isolated in patients before undergoing lung transplantation [13, 15, 19]. Otherwise the majority of authors agree to treat *Nocardia* species when, even though initially categorized as a colonizer, they are isolated in presence of: worsening of clinical status, radiological features or lung function or in cases where there is a concurrent infection with more common bacterial species in pwCF, such as Pa, and the patient does not improve despite broad antibiotic coverage [8, 10, 14, 15, 20, 21]. However, the eradication of *Nocardia* species is difficult to obtain [19]. In any case, most studies performed so far describe few cases of *Nocardia* infection in pwCF, and it is possible that the occurrence of such infection is underestimated due to its limited recognition and research in laboratories [9, 15, 23].

In conclusion, our study shows that, although in a few cases the isolation of *Nocardia* is directly associated with a deterioration in lung function, various cystic fibrosis centers around the world prefer to treat it immediately.

What antibiotic regimen should be used?

Antibiogram should drive the selection of the most effective therapy [11, 23]. Interestingly, the species that more frequently infect pwCF seem to not show difference in the pattern of susceptibility [15, 23] even if the identification of the species is rather difficult using conventional cultural and biochemical methods, and misclassifications may occur [4]. In most studies, trimethoprim-sulfamethoxazole was used as first-line treatment, followed by minocycline or amikacin in more severe forms [7–12,

14, 15, 19, 21, 23]. Linezolid, to which *Nocardia* is almost always susceptible, may be an alternative [14–21]. In case of worsening general clinical conditions, hospitalization is necessary along with the initiation of intravenous antibiotic therapy using at least two antibiotics chosen based on the antibiogram [14, 15, 21]. When combination therapy is required, drugs included can be third-generation cephalosporins, amikacin and imipenem [12, 13, 15, 19–23].

How long should the antibiotic treatment for *Nocardia* last?

It should be continued based on the severity of the pulmonary condition and the progression of antimicrobial susceptibility [3, 14, 15, 20, 21]. In the literature, treatments from 6 to 12 months are recommended for serious lung infections or in patients with strong immunosuppression. If symptoms are few, treatment could be reduced to 1–3 months [15].

Conclusions

Nocardia species are a complex group of organisms which can be isolated in pwCF. Of the validly described species, not all strains have been shown to be pathogenic in humans. Several species have been implicated as the cause of serious infections, especially in immunocompromised patients such as pwCF, but the identification of the specific *Nocardia* spp complex and expensive techniques available only in few laboratories. The picture is further complicated by the fact that *Nocardia* is not included in dedicated CF registries, so the care of these patients relies on individual experiences reported by centers located around the world and related reviews.

Several studies suggest that *Nocardia* acts mainly as a colonizer rather than a pathogen, not resulting in active infection, while other studies illustrate how *Nocardia* species could cause lung deterioration and promote the onset of other bacterial infections. In particular, patients with history of ABPA, those undergone lung transplantation or in therapy with steroids or immunosuppressor, are at a higher risk of clinically active Nocardiosis.

Management of nocardia isolation has no protocols validated by evidence-based medicine approach and under these circumstances our center, as well as others reported in this review, has chosen a pro-active approach and attempted eradication in the absence of symptoms as is done with other pathogens in pwCF.

In general the isolation of the bacteria does not necessarily imply therapy, but patients need to be monitored closely to assess the possible occurrence of active infection. On the contrary, the treatment is indicated in patients showing lung involvement with the possible appearance of pneumonia, pleural effusion, fever, cough, or a decrease in FEV₁, or in patients undergoing

pulmonary transplantation. However, the eradication of *Nocardia* is difficult to obtain. The complexity of *Nocardia*'s role in pwCF underscores the importance of individualized patient care and ongoing clinical monitoring.

Further research is needed to refine treatment strategies, identify definitive risk factors, and elucidate its impact on lung function, as well as defining the role of the lung microbiota on the risk of infection or the impact of new CFTR modulators. The possibility of improvement in CFTR function resulting in enhanced ability to clear pathogens, has attracted considerable attention and literature, in particular for *P. Aeruginosa* and *A. Fumigatus* [24, 25], and this possibility could radically change the prognosis of these patients with *Nocardiosis*.

Supplementary Information

The online version contains supplementary material available at <https://doi.org/10.1186/s12890-024-03217-0>.

Supplementary Material 1

Author contributions

All authors contributed to the concept and design of the systematic review for which this protocol has been written. TB and AC wrote the first draft of the manuscript. EC, VT, DD, SC and GT contributed to subsequent drafts. All authors reviewed and approved the final manuscript before submission.

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Data availability

All data generated or analysed during this study are included in this published article.

Declarations

Ethics approval and consent to participate

was obtained from the Ethical Committee of the CF Center of Florence (on November 14, 2023) and written informed consent for the clinical case publication was obtained by the patient.

Consent for publication

Non applicable.

Patient and public involvement

No patients or members of the public were directly involved in this research study.

Competing interests

The authors declare no competing interests.

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